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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/745,920	12/21/2000	Kenneth C. Parker	SYP-155 7783/571	2871

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EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 04/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/745,920	PARKER, KENNETH C.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-24 and 26-33* is/are pending in the application.

4a) Of the above claim(s) *30-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9-24, 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

KD

DETAILED ACTION

1. This application has been transferred to a new examiner.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 16 March 2005 has been entered.

Claim Rejections - 35 USC § 112

3. The rejections of claims 1-7, 9-24, and 26-29 under 35 U.S.C. 112, second paragraph in the Office action mailed 17 December 2004 is withdrawn in view of the amendment to the claims filed 16 March 2005.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14-15 are indefinite for recitation of the phrases "intense mass signals" and "intense biomolecule fragment count" because it is not clear if any intensity is being claimed. The rejection would be overcome by amendment of the claims to recite "mass signal intensity" and "biomolecule fragment intensity."

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 1-7, 9-24, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yates, III et al. in view of Gras et al. in view of Wright et al.

Yates, III et al. describe a method of using tandem mass spectrometry to determine sequences that are likely to be identical to an experimentally derived peptide (col. 2, lines 22-27). Yates, III et al. describe introducing an unknown peptide into a first mass spectrometer to separate it from the rest of the sample (col. 2, lines 54-64). The peptide and its fragments are then passed through a second mass spectrometer to obtain an intensity and mass-to-charge ratio (m/z) (col. 3, lines 4-7), which includes measuring mass signals and a mass spectrum of a biomolecule fragment as seen in Figure 5 (col. 3, lines 7-9). Yates, III et al. describe a method in Figure 2 where an unknown (12) is analyzed in a tandem mass spectrometer (14) to obtain

fragment spectrum (16) and compared (24) to the mass spectra (22) of proteins from a protein sequence library (20) on a computer. Yates, III et al. describe performing this comparison and calculating a closeness-of-fit measure or score for each of a plurality of mass spectra (col. 4, lines 9- 16). Yates, III et al. describe determining if a fragment mass is found in a measured fragment spectrum and scores are generated and sorted in a repeated cycle which results in one or more candidate amino acid sequences (col. 3, lines 21-28). Yates, III et al. describe high-scoring candidate sequences (col. 3, lines 29-30). Yates, III et al. describe a mass tolerance of the unknown peptide from which spectra from known sequences (i.e. potential source biomolecules) are identified if they fall within this tolerance amount (col. 4, lines 59-67 and Figure 4) which is reasonably interpreted as the biomolecule fragment detection parameter. Yates, III et al. describe an example using a tolerance of +0.05% of the mass of the unknown peptide used (col. 5, lines 25-26) which is reasonably interpreted as a detection efficiency as stated in claims 7 and 24. Yates, III et al. describe the high probability or likelihood that the unknown peptide has an identical amino acid sequence to one of the subsequences taken from the protein sequence library due to the high closeness-of-fit score with respect to the spectra comparison (col. 4, lines 16-23). Yates, III et al. further describe the high probability of the unknown protein and the known protein from the library as being identical or similar with subsequences with high closeness-of-fit scores (col. 4, lines 23-29). Yates, III et al. describe performing further MS-MS analysis if original scoring procedures do not delineate an answer of protein match (col. 8, lines 53-61) as stated in claim 23. Yates, III et al. describe the calculation of closeness-of-fit (56) in Figure 3 and then the selection of sequences with the highest scores (58). Yates, III et al. describe outputting matching data for sequences with the highest correlation function (62). Yates, III et al. describe

normalizing the spectrum (col. 4, lines 35-38) which is reasonably interpreted as a form of calibration as in instant claim 4. Yates, III et al. describe the above-mentioned procedure as being performed automatically on a computer (col. 4, lines 30-34). Yates, III et al. describe computational resources and storage facilities (col. 9, lines 24-49 and col. 21, lines 8-10) as stated in claims 28 and 29. Yates, III et al. describe identifying 200 of the most intense ions from the experimentally-derived fragment spectrum (col. 4, lines 44-45) as mentioned in claim 14. Yates, III et al. describe the calculation of closeness-of-fit (56) in Figure 3 and then the selection of sequences with the highest scores (58). Yates, III et al. describe outputting matching data for sequences with the highest correlation function (62) which suggests that any scores lower than the highest scores are likely absent and therefore are not outputted (also see Figure 6D) as stated in claim 2. Yates, III et al. do not teach correcting a mass intensity for an isotopic variant (claim 3), removing noise (claim 5), removing artificial background intensity (claim 6), weighted biomolecule scores, fragment counts, and signal intensity scores to determine the likelihood of the presence or absence of a biomolecule as well as determining a relative concentration based on the biomolecule score.

Gras et al. describe a program that identifies a protein based on mass spectra despite chemical modifications (abstract, lines 1-5) which could be an isotopic variant as stated in claim 3. Gras et al. also describe this determination of isotopic variants via software that often comes with the spectrometer (page 3538, col. 1, lines 1-5 and col. 1, third paragraph). Gras et al. describe a trend or baseline as the signal produced if no material entered the mass spectrometer and in the absence of noise (page 3537, col. 2, lines 10-14; page 3538, col. 1, lines 18-24; and Figure 1) which is reasonably interpreted as the removal of noise and background intensity as

stated in claims 5 and 6. Gras et al. describe the smoothing out of error functions related to the mass signals (page 3538, lines 21-26). Gras et al. describe using selected parameters to search proteins in a database that match the experimental spectra and assigning a score to the candidate protein (page 3541, col. 1, paragraph 2). Gras et al. describe the parameters' effects on the quality and efficiency of the identification (page 3541, col. 1, paragraph 3) as mentioned in claims 7 and 24. Gras et al. describe parameters that include the maximum distance between experimental and theoretical masses, the minimum number (or score) of matched peptides necessary for a protein to be selected, and the number of peaks returned by the peak detection program (page 3541, col. 1, paragraph 4). Gras et al. describe eliminating the least likely proteins in the list of candidates using parameters such as the minimum number of matched peptides or number of detected peaks, as well as depending on their thresholds (page 3541, col. 2, paragraph 1). Gras et al. describe the parameter of peak intensity in the mass spectrum as well (page 3542, col. 2, lines 40-44). Gras et al. describe a mass level parameter that characterizes the degree of match between the experimental mass and the peptide mass of the search library protein (page 3541, col. 1, paragraph 3) that is reasonably interpreted as a mass error. Gras et al. describe defining score calculations by determining the most important parameters, their relative weights and how to integrate them all into the score calculation (page 3542, col. 2, lines 20-23). Gras et al. describe counting the number of experimental masses matching theoretical peptide masses (page 3542, col. 2, lines 29-33) which are fragment counts. Gras et al. describe the concept of the more identified masses a protein has in the mass spectrum, the higher is the confidence for its identification (page 3542, col. 2, lines 33-35). Gras et al. describe assigning weights to each peptide mass, depending on the presence of a match resulting in a score calculation (page 3542,

col. 2, lines 36-41 and page 3543, col. 2, lines 15-19). Gras et al. describe taking into account the calibration error of the measuring device, eliminating masses that are too far from the regression line, and repeating this process when the previous masses were eliminated in the previous step (page 3543, col. 1, paragraph 3). Gras et al. describe identifying proteins via scores obtained of the proteins in a ranked list of candidate proteins (page 3543, col. 2, lines 37-41).

Wright et al. describe measurement of concentration in the mass spectrometer, its use in standardization of the process including relative estimates, and relative errors resulting without a calibration correction (col. 17, lines 6-26) as stated in claim 16.

Yates, iii et al. state that interpretation of the fragment spectra to produce candidate amino acid sequences is time-consuming, often inaccurate, and highly technical (col. 1, lines 52-59). Yates, III et al. note that relying on human interpretation often means that analysis is relatively slow and lacks strict objectivity (col. 1, lines 59-60). They further state that approaches based on peptide mass mapping are limited to peptide masses derived from an intact homogeneous protein generated by specific and known proteolytic cleavage (col. 1, lines 61-64). Yates, III et al. state that it would be useful to provide a system for correlating fragment spectra with known protein sequences in a fast and objective way (col. 1, lines 65-67). Yates, III et al. show a spectral interpreting method that could be used with any size peptide (col. 20, lines 59-60). However, Yates, III et al. note that certain variations and modifications could be made to their method. One of ordinary skill in the art would have been motivated to make further improvements to the identification method of spectral data, such as that stated by Yates, III et al. (col. 2, lines 5-27) in order to provide more accurate results as stated by Yates, III et al. (col. 1, lines 52-59). Therefore, it would have been obvious to one having ordinary skill in the art at the

time the invention was made to include features such as correcting a mass intensity for an isotopic variant, removing noise and artificial background intensity, creating weighted biomolecule scores, fragment counts, and signal intensity scores to determine the likelihood of the presence or absence of a biomolecule, as stated by Gras et al., as well as determining a relative concentration based on the biomolecule score, as stated by Wright et al., in order to provide precise and fast determination of peptide masses, even if the peaks are of low intensity and overlap (Gras et al., abstract, lines 6-7) and to provide accurate and precise concentration estimates (Wright et al., col. 17, lines 19-21) to create more accurate results in mass spectral identification, as stated by Yates, III et al. (col. 1, lines 52-59). Thus, Yates, III et al., in view of Gras et al. in view of Wright et al. motivate the limitations of claims 1-7, 9-24, and 26-29.

Response to Arguments

9. Applicant's arguments filed 16 March 2005 have been fully considered but they are not persuasive. As understood by the Office, the applicants state that the applied references do not show use of relative mass signal intensities produced by fragments of a molecule to identify a molecule from a mass spectrometry pattern. However a review of the claims shows that the clamed invention is drawn to an iterative method in which mass and intensity data of **single peaks** of a mass spectrometry pattern are combined with data of other peaks to identify a molecule from a mass spectrometry pattern. The use of relative intensities of multiple peaks is not claimed.

10. The applicants are invited to request an interview with the examiner to discuss possible allowable subject matter.

Conclusion

11. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center at (800) 786-9199.Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, PhD. can be reached on 571 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

John S. Brusca 16 April 2005

John S. Brusca
Primary Examiner
Art Unit 1631

jsb